# CHAPTER 2

## $C_2$-SYMMETRICAL *N*-HYDROXYSUCCINIMIDES AS CHIRAL DERIVATIZING AGENTS

### *2.1 Introduction*

There is a constant need for methods to determine the ratio of enantiomers in chiral non-racemic compounds. Before the mid-1960's, enantiomeric purity was usually assessed by using chiroptical methods. This involved measuring the optical rotation of a sample with a polarimeter. This value, called optical purity, is then compared to the known rotation for an enantiomerically pure sample. It is still a widely used method in organic chemistry. However, there are several sources of error in using this method. If the maximum rotation is unknown, it must be determined by some means. The literature is poisoned with examples of incorrect optical rotations for compounds considered to be enantiomerically pure.[1] A second problem with optical purity is the potential presence of a chiral impurity, which will cause an unsuspected error in the observed rotation. This is particularly serious when the impurity has a high rotation.

Therefore, simple and more reliable methods for determining enantiomeric purity have been developed. Although impressive progress has been made in developing sensitive and accurate GC and HPLC methods,[2] many organic chemists prefer to use NMR methods.[3] NMR analysis may be performed with chiral complexing reagents,[4] chiral lanthanide shift reagents[5] and chiral derivatizing agents (CDA's).[3]

Among the various chiral derivatizing agents, Mosher's reagent, table 2.1, is widely used.[6] The $\alpha$-methoxy-$\alpha$(trifluoromethyl)phenylacetic acid derivatives can be analyzed with $^1H$, $^{13}C$ and $^{19}F$ NMR. The acid chloride of Mosher's reagent reacts with primary and secondary alcohols or amines to form diastereomeric esters or amides.

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1 Weinges, K.; Dietz, V.; Oeser, T.; Irngartinger, H. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 680.

2 a) Schurig,V.; Nowotny, A.P. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 939. b) Okamato, Y.; Hatada, K. *J. Chromatogr.* **1987**, *389*, 95. c) Allenmark, S.G. *Chromatographic enantioseparation: Methods and Applications*, Ellis Horwood: Chichester, **1988**.

3 For some review articles on this issue see: a) Yamaguchi, S. In Morrison, J.D. *Asymmetric Synthesis*: Academic Press: New York, **1983**; vol. 1, chapter 7. b) Parker, D. *Chem. Rev.* **1991**, *91*, 1441. c) Hulst, R. Ph. D. Thesis Groningen, **1994**. d) Hulst, R.; Kellogg, R.M.; Feringa, B.L. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 115.

4 a) Shapiro, M.J.; Archinal, A.E.; Jarena, M.A. *J. Org. Chem.* **1989**, *54*, 5826 and references sited therein. b) Parker, D.; Fulwood, R. *Tetrahedron: Asymmetry* **1992**, *3*, 25.

5 Fraser, R.R. In Morrison, J.D. *Asymmetric Synthesis*; Academic Press: New York, **1983**: Vol. 1 Chapter 9.

6 a) Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543. b) Dale, J.A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

Despite the success of Mosher's reagent as CDA, several new CDA's have been developed. A selection of commonly used CDA's is summarized in table 2.1. The enantiomeric purity is determined via $^{1}H$, $^{13}C$, $^{19}F$ and $^{31}P$ NMR methods. Several of the examples listed in table 2.1 have been developed in our laboratory.

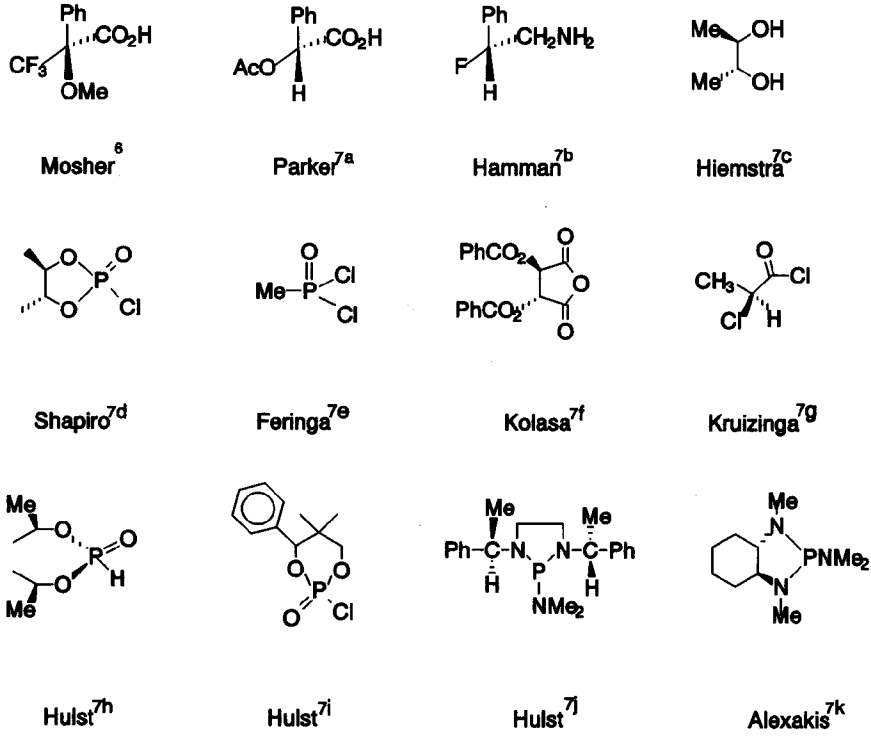


*Table 2.1. Common chiral derivatizing agents*

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[7] a) Parker, D.J. *J. Chem. Soc. Perkin Trans 2* **1983**, 83. b) Hamman, S.J. *J. Fluorine Chem.* **1989**, *45*, 377. c) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183. d) Anderson, R.C.; Shapiro, N.J. *J. Org. Chem.* **1984**, *49*, 1304. e) Feringa, B.L.; Smaardijk, A.; Wynberg, H. *J. Am. Chem. Soc.* **1985**, *107*, 4798. f) Kolosa, T.; Miller, M.J. *J. Org. Chem.* **1986**, *51*, 3055. g) Kruizinga, W.H.; Bolser, J.; Kellogg, R.M.; Kamphuis, J.; Boesten, W.H.J.; Meÿer, E.M.; Schoenmaker, H.E. *J. Org. Chem.* **1988**, *53*, 1826. h) Hulst, R.; de Vries, K.; Feringa, B.L. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1092. i) Hulst, R.; Zijlstra, R.W.J.; Feringa, B.L.; de Vries, N.K.; ten Hoeve, W.; Wynberg, H. *Tetrahedron Lett.* **1993**, *34*, 1339. j) Hulst, R.; de Vries, N.K.; Feringa, B.L. *Tetrahedron: Asymmetry* **1994**, *5*, 699. k) Alexakis, A.; Mutti, S.;

It is noteworthy that many of the CDA's are developed for analysis of chiral amines or alcohols, but there are relatively few reports of useful CDA's for carboxylic acids.[8] Chiral derivatizing agents based on α-phenylethylamine or α-naphtylethylamine have been reported, but these methods often require in addition an achiral shift reagent. More useful are (S)-methylmandelate[9] and 2-fluoro-2-phenylethylamine.[7b] But no good, reliable CDA for determining the enantiomeric purity of carboxylic acids is available.[10] Our intention was to develop a generally applicable CDA for the determination of enantiomeric purity of carboxylic acids. The combination of dibenzoyltartaric acid anhydride as CDA for amines, hydroxylamines, amino acids and peptides[7f] and the use of *N*-hydroxysuccinimides in peptide synthesis[11] made us realize that chiral *N*-hydroxysuccinimides derived from tartaric acid, such as **201** might serve as CDA, figure 2.1. The corresponding diacetoxy derivative of **201** has been used in enantioselective peptide synthesis [11a].

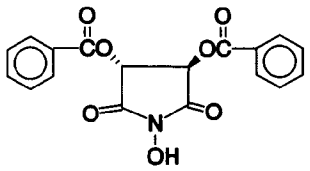

*Figure 2.1 N-hydroxy-3,4-dibenzoyl-2,5-pyrrolidinedione 201*

We will discuss the synthesis and use of these novel chiral $C_2$-symmetrical *N*-hydroxysuccinimides as CDA for the enantiomeric purity determination of carboxylic acids by means of $^1$H-NMR.

## *2.2 Synthesis of N-hydroxysuccinimides derived from tartaric acid*

We synthesized two novel chiral *N*-hydroxysuccinimides as outlined in scheme 2.1. Cyclisation of tartaric acid with 3.2 equivalents of the appropriate acid chloride afforded

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Mangeney, D. *J. Org. Chem.* **1992**, *57*, 1224.

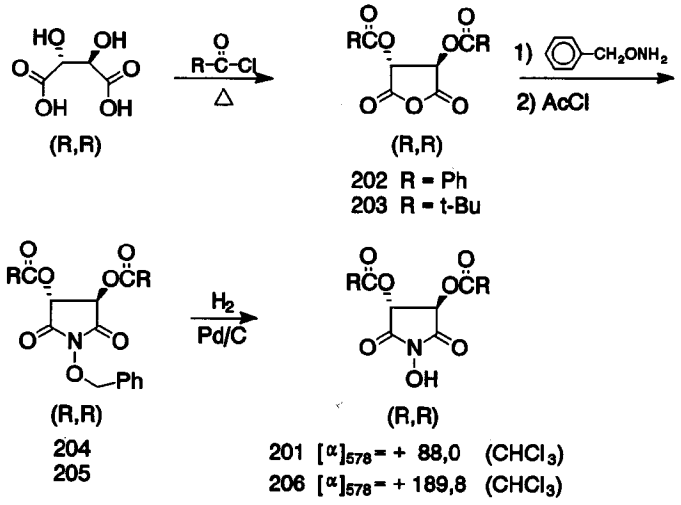
[8] a) Feringa, B.L.; Wynberg, H. *J. Org. Chem.* **1981**, *46*, 2547. b) Moorlag, H.; Kruizinga, W.H.; Kellogg, R.M. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 479.

[9] a) Brown, J.M.; Parker, D. *J. Org. Chem.* **1982**, *97*, 2722. b) Baker, K.V.; Brown, J.M.; Cooley, N.A.; Hughes, G.D.; Taylor, R.J. *J. Organometal. Chem.* **1989**, *370*, 397.

[10] a) Parker has used 1,2-diphenyl-diaminoethane as a chiral solvating agent for direct NMR assay of enantiomeric purity of carboxylic acids. Fulwood, R.; Parker, D. *Tetrahedron: Asymmetry* **1992**, *3*, 25. b) Recently another CDA has been developed: Brown, E.; Chevalier, C.; Huet, F.; Le Grumelec, C.L.; Lézé, A.; Touet, J. *Tetrahedron Asymmetry* **1994**, *5*, 1191.

[11] a) Teramoto, T.; Dequchi, M; Kurosaki, T. *Tetrahedron lett.* **1981**, *22*, 1109. b) Anderson, G.W.; Zimmerman, J.E.; Callahan, F. *J. Am. Chem. Soc.* **1963**, *85*, 3039.

the corresponding anhydrides **202** and **203** in high yield, following a literature procedure[12]. Treatment of these anhydrides with benzyloxyamine in THF at 0°C gave the half amide, which on cyclisation with acetyl chloride furnished imides **204** and **205**. The *O*-benzyl protected *N*-hydroxysuccinimides are highly crystalline compounds. Deprotection with $H_2$/Pd/C afforded the *N*-hydroxysuccinimides **201** and **206** as white solids.




*Scheme 2.1. Synthesis of N-hydroxysuccinimides derived from tartaric acid*

The synthesis is easily performed on a molar scale. The starting materials are readily available and all intermediates are crystalline compounds, which makes purification easy. The *N*-hydroxysuccinimides **201** and **206** are stable compounds and can be stored for years without decomposition.

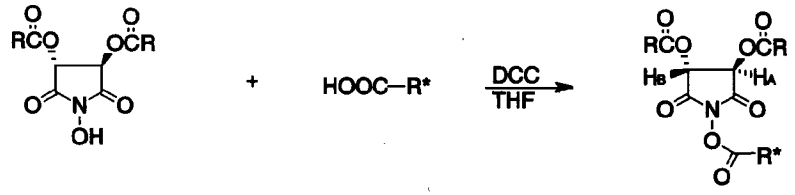
### *2.3 N-hydroxysuccinimides 201 and 206 as CDA for carboxylic acids*

The formation of esters used in the ee determination of chiral carboxylic acids must, for obvious reasons, occur under conditions which exclude the possibility of racemization[13] or kinetic resolution. The formation should proceed without using high temperature, long reaction times or tedious reaction conditions. Work-up has to be easy and the esters may not be purified by crystallization. The coupling reaction of *N*-

[12] a) Shriner, R.L; Furrow, R. *Org. Synth. Coll. Vol. IV.* **1963**, 242. b) Bulter, C.L.; Cretcher, L.H. *J. Am. Chem. Soc.* **1933**, *55*, 2605. c) Duhamel, L.; Angibaud, P.; Ple, G.; Desmurs, J.R. *Synth. Commun.* **1993**, *23*, 2423.

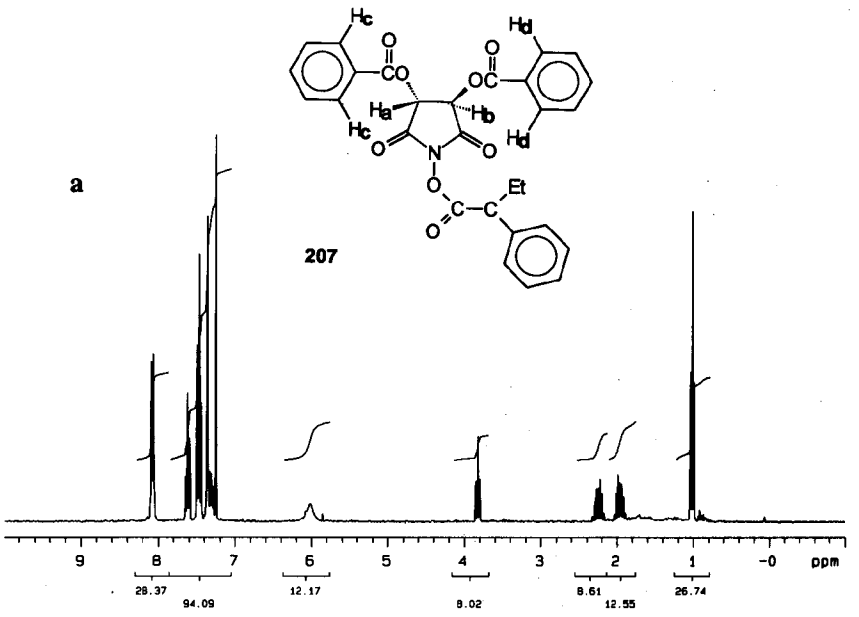
[13] *N*-Hydroxysuccinimide is used in peptide synthesis to prevent racemization of amino acids.

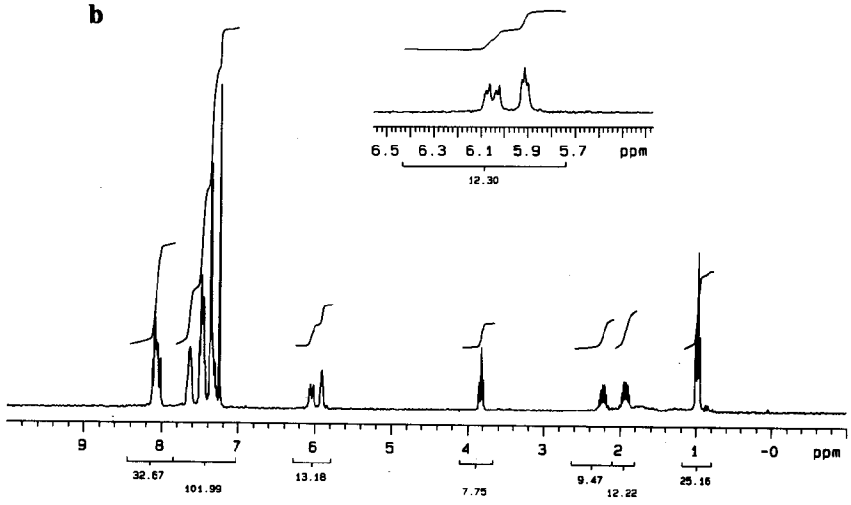
hydroxysuccinimides **201** and **206** with carboxylic acids providing esters **207** and **208** is depicted in scheme 2.2. The procedure is straightforward: a mixture of one equivalent of carboxylic acid, one equivalent N-hydroxysuccinimide **201** or **206** and dicyclohexylcarbodiimide(DCC) in THF is stirred for one hour. The dicyclohexylurea (DHU) is removed by filtration over silica and the solvent is evaporated. In all cases, the esters **207** and **208** were obtained as white solids, in quantitative yield.




*Scheme 2.2. Coupling reaction of N-hydroxysuccinimides 201 or 206 with chiral acids*

The first acid we examined was 2-phenylbutyric acid. All three possible esters (racemic, R(-) and S(+)) were prepared in quantitative yield and analyzed by $^1$H-NMR. Figure 2.3a shows the $^1$H-NMR of racemic 2-phenylbutyric acid coupled to (3R,4R)-3,4-bisbenzoyl-*N*-hydroxysuccinimide (**201**) at room temperature.




b
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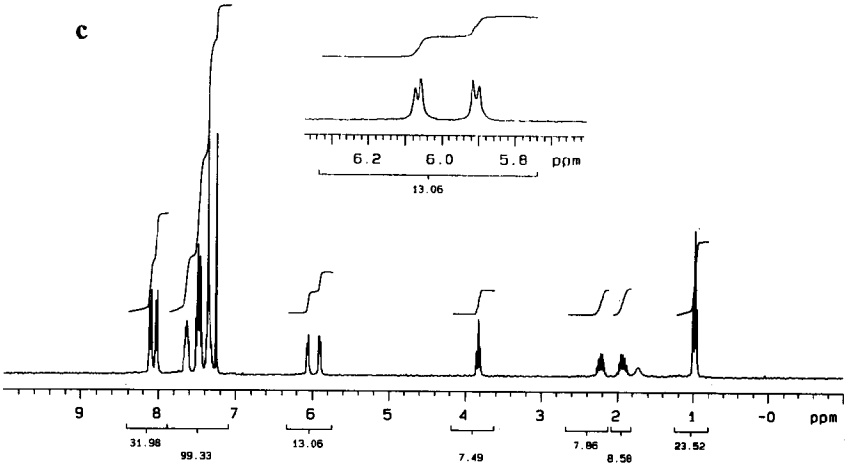
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13.06
7.49
7.86
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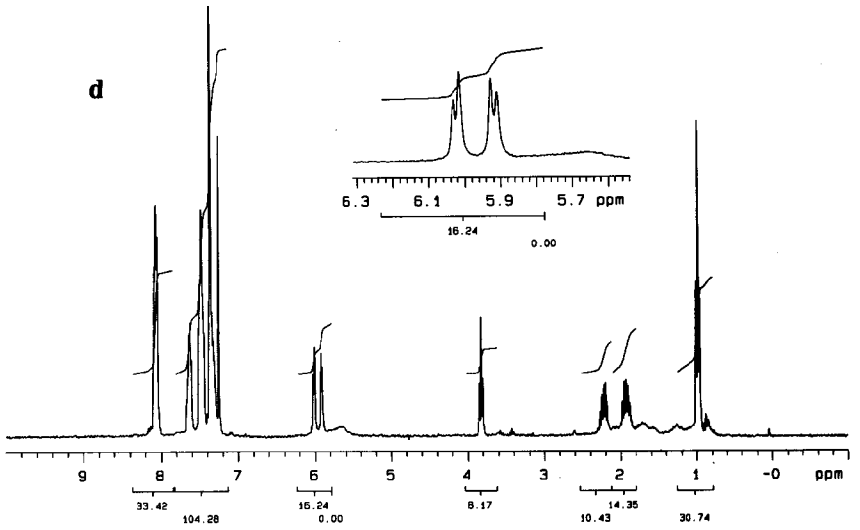
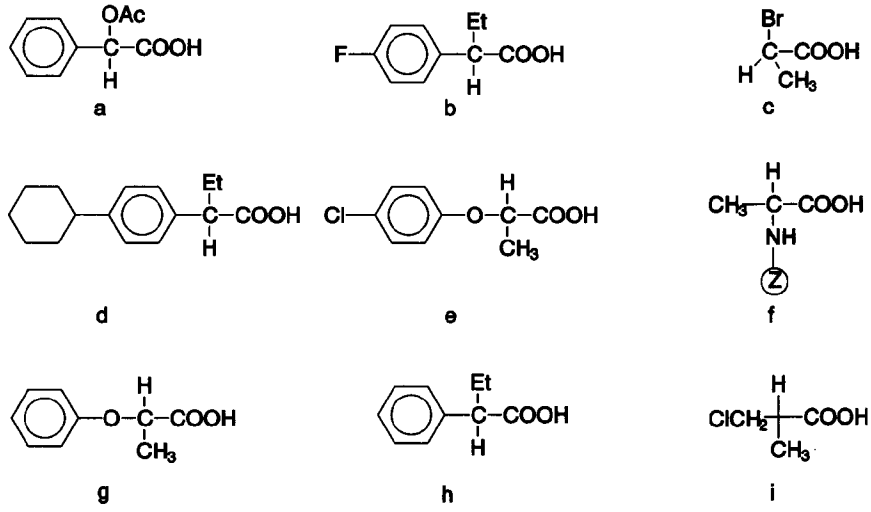



*Figure 2.3 $^1$H-NMR spectra of 2-phenylbutyric acid coupled to CDA 201 in $CDCl_3$; a) racemic 2-phenylbutyric acid at RT; b) racemic 2-phenylbutyric acid at -30°C; c) (R)-2-phenylbutyric acid at -30°C d) (S)-2-phenylbutyric acid at -30°C.*

It is noticed that the signal for the $H_A$ and $H_B$ protons in **207**, at $\delta$ 6 ppm is very broad,figure 2.3a. Raising the temperature to 60°C a sharp singlet was observed. On lowering the temperature to -30°C a totally different spectrum was obtained, figure 2.3b. The whole system is conformational locked and the signals for the $H_A$ and $H_B$ protons are split into a double AB system. Distortion of the $C_2$-symmetry of the pyrrolidinedione ring system created by reaction with a chiral acid has made the homotopic protons $H_A$ and $H_B$ heterotopic.[14] The singlet observed in **201** is changed into an double AB system for **207**. The double AB system in figure 2.3b is created by the two diastereoisomers formed. The $^1$H-NMR spectra recorded of -30°C of optically pure (R) and (S)-2-phenylbutyric acid coupled to **201** are shown in figure 2.3c and 2.3d respectively. In these cases an AB system for the $H_A$ and $H_B$ protons is observed. Integration of the two separate doublets at $\delta$ 6.08 and 6.02 ppm for the (R) and (S) enantiomer respectively allows the determination of the enantiomeric purity of 2-phenylbutyric acid. The $^1$H-NMR shows another remarkable fact, namely that the ortho protons $H_C$ and $H_D$ of the phenyl ring at $\delta$ 8.15 ppm also become hetereotopic, creating double doublets for the optically pure esters, figure 2.3c and 2.3d and four doublets for the racemic ester, figure 2.3b. Even although

[14] When recording a $^1$H-NMR of **201** or **206** at -30°C, only one signal was observed for the homotopic protons $H_A$ and $H_B$, proving the $C_2$-symmetry.

the chiral centra in ester **207** are separated by 5 bonds, both diastereoisomers can be observed by $^1$H-NMR at -30°C.




*Scheme 2.3. Carboxylic acids used in the $^1$H-NMR analysis with CDA's 201 and 206*

The results obtained with a variety of carboxylic acids are summarized in table 2.2. Although the best results were obtained at -30°C, some entries (1,15 and 17) also gave peak separation at room temperature. The chemical shift differences of the doublets, observed for the $H_A$ and $H_B$ resonances generally ranges from 0.03 to 0.2 ppm, but are always baseline separated. Other resonances within the esters **207** and **208** may also provide diastereomeric peak separation. No significant differences were observed between CDA's **201** and **206**.

These observations indicate that, within NMR detection limits, the chiral $C_2$-symmetrical N-hydroxysuccinimides **201** and **206** can be used in the determination of the enantiomeric excess of carboxylic acids by $^1$H-NMR.[15]

[15] We checked this by comparison of samples with known enantiomeric composition determined by polarimetry and $^1$H-NMR.

**Table 2.2.** **$^1$H-NMR data for diastereoisomeric esters 207 and 208.**

| entry | CDA | substrate | δ(ppm) | Δδ(ppm) |
|---|---|---|---|---|
| 1 | **206** | a (rac) | 5.58-5.66 | 0.08 |
| 2 | **206** | a ( - ) | 5.58 | |
| 3 | **206** | b (rac) | 5.72-5.76 | 0.04 |
| 4 | **206** | b ( + ) | 5.76 | |
| 5 | **206** | b ( - ) | 5.72 | |
| 6 | **206** | d (rac) | 5.67-5.70 | 0.03 |
| 7 | **206** | d ( + ) | 5.70 | |
| 8 | **206** | d ( - ) | 5.67 | |
| 9 | **206** | e (rac) | 5.67-5.77 | 0.1 |
| 10 | **201** | f (rac) | 6.08-6.15 | 0.07 |
| 11 | **201** | f ( - ) | 6.08 | |
| 12 | **201** | h (rac) | 6.02-6,08 | 0.06 |
| 13 | **201** | h ( + ) | 6.08 | |
| 14 | **201** | h ( - ) | 6.02 | |
| 15 | **201** | a (rac) | 6.00-6.08 | 0.08 |
| 16 | **201** | a ( - ) | 6.00 | |
| 17 | **201** | g (rac) | 5.94-6.14 | 0.2 |
| 18 | **201** | c (rac) | 6.04-6.08 | 0.04 |
| 19 | **201** | i (rac) | 6.07-6.10 | 0.03 |

*The indices refer to scheme 2.3; entries 12,13 and 14 refer to the spectra in figure 2.3; the resonances observed are for the $H_A$ and $H_B$ protons.*

## *2.4 Conclusions*

We have described a convenient method for the synthesis of $C_2$-symmetrical chiral *N*-hydroxysuccinimides derived from tartaric acid. These compounds **201** and **206** are useful chiral derivatives agent for the determination of the enantiomeric excess of carboxylic acids by $^1$H-NMR. The method is quite attractive because, a) the esters are easily prepared and b) the NMR signals appear in an area of the spectrum (δ 5.5-6.2 ppm) generally unobscured by other resonances.

## 2.5 *Experimental section*

### General remarks

All experiments were performed under an inert ($N_2$) atmosphere when necessary. All solvents were used without further purification, unless otherwise noted. All commercially available chemicals were obtained from Janssen Chimica (Acros), Aldrich or Fluka and were used without further purification. Melting points (uncorrected) were determined on a Mettler FP-2 melting point apparatus, equipped with a Mettler FP-21 microscope. Optical rotations were determined at room temperature using a Perkin-Elmer 241 polarimeter and are given in units of $10^{-1}$ deg $cm^2$ $g^{-1}$. All rotation were determined with a concentration of c=1. $^1$H-NMR spectra were recorded on a Varian Gemini-200 (200MHz) or on a Varian VXR-300 spectrometer (at 300 MHz). For 200 and 300 MHz spectra the $^1$H-NMR and $^{13}$C-NMR chemical shifts are determined relative to the solvent ($CDCl_3$, unless otherwise noted) and converted to the TMS scale using $\delta(CDCl_3)$ = 7,26 ppm and 76,9 ppm. $^{13}$C-NMR spectra were recorded in the APT mode on either a Varian Gemini 200 (50.32 MHz) or Varian VXR-300 (75.48 Hz) spectrometer. Splitting patterns for $^1$H-NMR are designed as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet) and br (broad). For $^{13}$C-NMR the spectra are designed giving a positive value for the C and $CH_2$ peaks and a negative value for the CH and $CH_3$ peaks. Exact mass determinations were carried out on an AFJ-MS-902 spectrometer by Mr. A. Kieviet. Elemental analyses were performed in the micro analytical section of our department by Mr. H. Draaijer, Mr. J. Ebels and Mr. J. Hommes. The X-ray analysis was performed by Mr. F. van Bolhuis.

**(3*R*,4*R*)-3,4-Dibenzoyloxydihydro-2,5-furandione (202)** was prepared according to the procedure described in chapter 5. Yield 93%; mp 192-193°C (lit.[12] 173°C); $^1$H-NMR: $\delta$ 6.1 (s,2H), 7.5 (t,4H), 7.6 (t,2H), 8.1 (d,4H); $^{13}$C-NMR: $\delta$ 72.79 (CH), 127.04 (C), 128.69 (CH), 130.23 (CH), 134.53 (CH), 163.33 (C=O), 165.32 (C=O).

**(3*R*,4*R*)-3,4-Dipivaloyloxydihydro-2,5-furandione (203)** was prepared according to the procedure described in chapter 5. Yield 80%; $^1$H-NMR: $\delta$ 1.25 (s,18H), 5.6 (s,2H); $^{13}$C-NMR: $\delta$ 26.64 ($CH_3$), 72.18 (CH), 163.46 (C=O), 170.61 (C=O).

**(3*R*,4*R*)-*N*-Benzyloxy-3,4-dibenzoyloxy-2,5-pyrrolidinedione (204)**
A mixture of benzyloxyamine·HCl (25 g, 0,156 mol) and diethylamine (50 ml) in THF (200 ml) was stirred vigorously for 3 hours and filtered. The diethylamine·HCl salt was washed with THF (100 ml). The combined filtrates were cooled in a ice-water bath and anhydride **202** (53,04 g, 0,156 mol) was added portionwise. The resulting solution was stirred for 5 hours and concentrated to afford a white solid. To this solid was added AcCl (300 ml), the mixture was refluxed for 3 hours and excess AcCl was removed. The crude product was dissolved in EtOAc, washed with $H_2O$, 10% $NaHCO_3$ and dried ($Na_2SO_4$). Evaporation and crystallization from MeOH yielded 53,4 g (75%) of **204**. mp 105,7-

106,4°C; $[\alpha]_D$= + 147° ($CH_2Cl_2$); $^1$H-NMR: δ 5,18 (dd,2H), 5,64 (s,2H), 7,25-7,6 (m,11H), 8,0 (d,4H); $^{13}$C-NMR: δ 71,50 (CH), 79,3 ($CH_2$), 127,68 (C), 128,5 (CH), 129,5 (CH), 129,99 (CH), 130,08 (CH), 132,75 (C), 134,08 (CH), 169,52 (C=O), 165,3 (C=O); Anal. calc. for $C_{25}H_{19}O_7N$: C 67.40; H 4.30; N 3.15 Found: C 67.41; H 4.43; N 3.15; HRMS calc. for $C_{25}H_{19}O_7N$: 445,116 Found: No exact mass could be determined due to elimination of the benzoyl group (105) as indicated by the M/e 340 peak.

**(3*R*,4*R*)-*N*-Benzyloxy-3,4-dipivaloyloxy-2,5-pyrrolidinedione (205)** was prepared in the same as described for **204**. Yield 85%; mp 113,5-114,2°C; $[\alpha]_{578}$= +108,6° ($CH_2Cl_2$); $^1$H-NMR: δ 1,2 (s,18H), 5,1 (dd,2H), 5,25 (s,2H), 7,35-7,45 (m,5H); $^{13}$C-NMR δ: 26,74 ($CH_3$), 38,69 (C), 70,93 (CH), 79,17 ($CH_2$), 128,46 (CH), 129,47 (CH), 129,93 (CH), 132,74 (C), 164,63 (C=O), 177,18 (C=O); Anal. calc. for $C_{21}H_{27}NO_7$: C 62.19; H 6.72; N 3.46 Found: C 62.57; H 6.78; N 3.39; HRMS calc. for $C_{21}H_{27}O_7N$: 404,171 Found: No exact mass could be determined due to elimination of the pivaloyl group (91).

**(3*R*,4*R*)-*N*-Hydroxy-3,4-dibenzoyloxy-2,5-pyrrolidinedione (201)**
A suspension of imide **202** (15 g, 33 mmol) and Pd/C (10%)(1 g) in MeOH (200 ml) was hydrogenated for 2 hours. The catalyst was removed by filtration and the filtrate evaporated. The crude product was crystallized from $CH_2Cl_2$/octane to afford **201** as a white solid. Yield 11,5 g (98%); mp 150-152°C; $[\alpha]_{578}$= + 189,9° ($CHCl_3$); $^1$H-NMR: δ 5,8 (s,2H), 6,4-7,0 (br,OH), 7,25-7,6 (m,6H), 8,0 (d,4H); $^{13}$C-NMR: δ 66,64 (CH), 123,47 (CH), 125,12 (CH), 128,9 (CH), 160,43 (C), 160,52 (C=O); Anal. calc. for $C_{18}H_{13}O_7N$: C 60.83; H 3.69; N 3.94. Found: C 60.63; H 3.80; N 3.91; HRMS calc. for $C_{18}H_{13}O_7N$: 335,069 Found: No exact mass could be determined due to elimination of the benzoylgroup.

**(3*R*,4*R*)-*N*-Hydroxy-3,4-dipivaloyloxy-2,5-pyrrolidinedione (206)** was
prepared in the same manner as described for **201**. Yield (90%);mp 171-174°C; $[\alpha]_{578}$= +88° ($CHCl_3$); $^1$H-NMR: δ 1,25 (s,18H), 5,4 (s,2H), 7,4-8,0 (br,1H); $^{13}$C-NMR: δ 26,78 ($CH_3$), 38 (CH), 71,05 (CH), 165,6 (C=O), 178 (C=O); Anal. calc. for$C_{14}H_{21}O_7N$: C 53.33; H 6.71; N 4.44 Found: C 53.14; H 6.79; N 4.40; HRMS calc. for $C_{14}H_{21}O_7N$: 315,132 Found: 315,132.

**Typical procedure for the determination of the enantiomeric excess of carboxylic acids by use of reagents 201 and 206.**
To a solution of carboxylic acid (1 eq.) and reagent **201** or **206** (1 eq.) in THF was added DCC (1 eq.). The mixture was stirred for an hour and the DHU was removed by filtration over silica. The filtrate was evaporated to afford **207** or **208** as white solids. The solid was dissolved in $CDCl_3$ and a $^1$H-NMR was taken at -30°C to determine the enantiomeric excess.

Spectroscopic data for representative example of **207.** Ester depicted in figure 2.3 (-)2-phenylbutyric acid . mp 162-164°C; $^1$H-NMR: see figure 2.3; $^{13}$C-NMR: 11,71 ($CHCl_3$; 26,93 ($CH_2$); 50,27 (CH); 71,30 (CH); 127,56 (C); 127,8 (CH); 127,85 (CH); 128,46

(CH); 128,7 (CH); 130,11 (CH); 134,04 (CH), 136,18 (C); 162,61 (C=O); 165,02 (C=O); 168,77 (C=O); HRMS calc. for 501,142 Found: 501,142.